REMARKS

Claims 7 and 38-54 are pending. The Examiner has stated that Claim 7 is allowable, and maintains the rejection of Claims 38-54. Applicants respond below to the specific rejections of Claims 38-54 set forth in the Office Action. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 103(a) - the '066 Patent, the '401 Patent, the '772 Patent, the '129 Patent, the '304 Patent, Brand Miller et al, and Chung et al.

The Examiner has rejected Claims 38-54 as allegedly being unpatentably obvious over the '066 or '401 patents in view of the '772 patent, the '129 patent, the '304 patent, Brand-Miller et al. (1994) *Am. J. Clin. Nutr.* 59 (Suppl)747S-752S, and Chung et al. (2000) *J. Food Sci.* 5(1): 42-47.

According to the Examiner, the '066 and '401 patents teach pharmaceutical compositions comprising chromic tripicolinate and biotin for reducing hyperglycemia and stabilizing serum glucose levels. The Examiner argues that the '772 patent teaches that diabetes is the cause of hypercholesterolemia, that the '129 patent teaches compositions comprising chromium and biotin are effective in lowering LDL and triglycerides, that Brand Miller teaches that ranking foods on their glycemic index results in measurable clinical gains, and that the '304 patent teaches that insulin resistance due to hyperinsulinemia is commonly associated with increased triglycerides, decreased HDL and elevated body fat. Finally, the Examiner argues that Chung et al. discloses that biotin-rich ingredients lowered serum LDL, lowered serum triglycerides and increased serum HDL. According to the Examiner, in view of the teachings of the cited art, "it is expected . . .that the combination of chromium complex and biotin-rich ingredients would result in increased HDL cholesterol levels." *Office Action* at 3. The Examiner further maintains that the rejection is "not based solely on treatment of an underlying disease," *i.e.*, hyperglycemia and/or insulin resistance. *Id.* Applicants respectfully disagree.

According to currently applicable case law, to establish a *prima facie* case of obviousness, the prior art must teach or suggest all the claim limitations and there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Assuming the Examiner sets forth a valid *prima facie* case of obviousness, the Examiner must consider any rebuttal evidence, including evidence of unexpected results. A greater than

expected result, for example, demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating synergism) is evidence that the combination is non-obvious. *In re Antonie* 559 F.2d 618, 620 (CCPA 1977). A showing of unexpected results is usually sufficient to overcome a *prima facie* case of obviousness. *In re Albrecht,* 514 F.2d 1389, 1396 (CCPA 1975), M.P.E.P. §2145. A rejection under 35 U.S.C. § 103(a) can only be maintained where the Examiner has articulated a valid *prima facie* obviousness case, and where the applicant has not provided evidence sufficient to rebut the *prima facie* case.

Applicants respectfully submit that the references fail to support a *prima facie* case of obviousness. Specifically, the references relied upon by the Examiner do not teach or fairly suggest the combination of "a synergistically effective dose of chromium and biotin" to "raise serum HDL levels" as recited in Applicants' claims. Briefly, both the '066 and '401 patents relate to methods of reducing hyperglycemia and stabilizing serum glucose levels. '066 and '401 patents do not mention serum HDL levels. Furthermore, the skilled artisan would not reasonably expect that a treatment for hyperglycemia would be useful in raising serum HDL levels. Impaired HDL levels and heightened serum glucose levels/hyperglycemia are two independent conditions. As previously discussed, compositions useful in treating one condition (*i.e.*, hyperglycemia) are not always beneficial in treating the other condition (*i.e.*, impaired lipid profile). *See,* Amendment and Response filed March 15, 2007 at page 7. In particular, compositions useful in reducing hyperglycemia and stabilizing serum glucose, *e.g.*, pioglitazone, metformin and rosiglitzone, do not affect, or even exacerbate cholesterol and/or triglyceride levels. As such, it is clear that the underlying mechanisms of the two disorders are not one and the same, and there is no reasonable expectation that any composition that has beneficial effects in treating hyperglycemia would also be useful in raising serum HDL levels.

The secondary references, alone or in combination with the '066 patent, the '401 patent, or each other fail to teach or suggest the use of chromium and biotin to raise serum HDL levels. The '772 patent relates to chromium picolinate and uses thereof. The '772 patent does not mention biotin, and therefore cannot teach or suggest the synergistic benefits of combining chromium and biotin for raising serum HDL levels. Brand-Miller relates to calculating the glycemic index of food. Brand-Miller is silent regarding the use of chromium or biotin, and therefore cannot teach or suggest combining chromium and biotin to raise serum HDL levels.

The '129 to Rath patent does not provide the necessary teachings to render the claims *prima facie* obvious. Specifically, Rath teaches that a multivitamin that includes chromium and biotin, among several other ingredients, is useful for lowering Lipoprotein(a) plasma levels, lowering total cholesterol, lowering LDL cholesterol, and lowering triglycerides. There is nothing in Rath that would lead the skilled artisan to believe that chromium and biotin can be used together to synergistically raise serum HDL levels. The '304 patent relates to pharmaceutical compositions for the reduction of hyperinsulinemia. The '304 patent is silent regarding chromium and biotin, and therefore cannot teach or suggest using the combination of chromium and biotin to raise serum HDL levels.

Finally, the Chung et al. reference teaches that foods that have as active ingredients calcium, thiamin, riboflavin, ascorbate, biotin, and zinc raise serum HDL levels. *See,* Chung et al. at 43, Col. 1. The skilled artisan would not, however, ascertain that biotin alone has a beneficial effect on serum HDL levels. Rather, several of the ingredients are known to affect serum HDL levels present in the "foods" described by Chung et al. For example ascorbate is known to raise serum HDL levels. *See,* Burr, et al. (1982) Hum. Nutr. Clin. Nutr. 36(2):135, abstract, submitted herewith as **Exhibit A.** Likewise, calcium supplementation is known to increase serum HDL levels. *See,* Jacqmain, et al. (2003) Am. J. Clin. Nutr. 77:1448-52, submitted herewith as **Exhibit B.** Similarly, zinc is associated with increases in HDL cholesterol levels. *See,* Koo, et al. (1983) Am. J. Clin. Nutr. 37(6):918, abstract, submitted herewith as **Exhibit C.** Accordingly, the skilled artisan would not attribute the alleged increase in HDL levels reported by Chung et al. to biotin, which is present in a much lower concentration than the other components of the "active ingredient," which were also known to raise serum HDL levels. In other words, the skilled artisan could not determine what, if any, effect biotin had on serum HDL levels from the Chung et al. study.

In short, the combined teachings of the '066 or '401 patents, in view of the '772 patent, the '129 patent, Brand Miller, the '304 patent and Chung et al. fail to teach or suggest the combination of chromium and biotin (in amounts that synergistically raise serum HDL levels) to raise serum HDL levels. Accordingly, the references do not support a *prima facie* case of obviousness.

Furthermore, even if the Examiner established a *prima facie* case that Claims 38-54 were obvious over the cited references, Applicants' evidence of unexpected, synergistic results is sufficient to rebut the evidence of obviousness. *See, In re Antonie* 559 F.2d 618,620 (CCPA 1977). The data in the specification illustrates the synergistic effects of chromium and biotin on changes in HDL levels. In particular, Figure 14 illustrates that all combinations of chromium and biotin tested synergistically, elevated serum HDL levels (i.e., low chromium/low biotin; low biotin/high chromium; high biotin/low chromium; and high biotin/high chromium), when compared to the same doses of the compounds administered alone. As indicated in paragraph [0110], the nutrients were administered via daily water feeding at a specified dose/kg body weight. Applicants previously provided a Declaration of James Komorowski, which further explains the data in Figure 14. The Declaration states that "Low Chromium" or "LC" treatments were 1μg Cr/kg, *i.e.*, approximately 60 μg chromium per day for an average individual. "High Chromium" or "HC" treatments were 10μg Cr/kg, *i.e.*, approximately 600μg chromium per day for an average individual. "Low Biotin" or "LB" treatments were 30μg biotin/kg, *i.e.*, approximately 1,800μg biotin per day for an average individual. "High Biotin" or "HB" treatments were 300μg biotin/kg, *i.e.*, approximately 18,000μg biotin per day for an average individual. The synergistic effect on serum HDL levels could not have been predicted from the teachings of the cited art, and the unexpected results are sufficient to rebut any *prima facie* case of obviousness under 35 U.S.C. § 103(a).

For the reasons set forth above, the rejection of Claims 38-54 is improper. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Co-Pending Applications of Assignee

Applicant wishes to draw the Examiner's attention to the following co-pending applications of the present application's assignee.

Serial Number	Title	Filed
11/136,794	CHROMIUM/BIOTIN TREATMENT OF DYSLIPIDEMIA AND DIET-INDUCED POST PRANDIAL HYPERGLYCEMIA	May 24, 2005

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 1/22/08

By: _____

Mallary K. de Merlier
Registration No. 51,609
Attorney of Record
Customer No. 20,995
(619) 235-8550

4616189
120507